PATENTS

A qualitative study of biosimilar manufacturer and regulator perceptions on intellectual property and abbreviated approval pathways

Abbreviated regulatory approval pathways for biosimilars were created to accommodate intellectual property protection, foster competition and lower drug prices, but their success in achieving these goals has been mixed.

Biologic drugs are complex molecules derived from living systems[1] and constitute a growing and costly segment of the pharmaceutical market[2,3]. Globally, expenditures on biologics totaled $277 billion in 2017 and are forecast to rise to $452 billion by 2022[4]. This spending has been driven primarily by high biologic drug prices, which often exceed $100,000 per patient per year in the United States[5,6].

Recent creation of abbreviated approval pathways in the European Union and United States for biosimilars — products that are similar to an originator biologic with regard to quality, safety and efficacy — was intended to help lower spending on biologics drugs by fostering competition following the originator biologic's loss of market exclusivity[7]. However, the success of biosimilars in meeting this aim has been mixed. As of 1 May 2020, the US Food and Drug Administration (FDA) had approved 26 biosimilars for 9 originator biologics[8], of which 14 have launched[9]. By contrast, the European Medicines Agency (EMA) had approved 64 biosimilars for 16 originator biologics[10], with price reductions per treatment day varying widely across therapeutic class, from 3% for oncology treatments to 30% for epoetins[11]. Thus, expected widespread price reductions from biosimilar entry have not yet materialized in either the United States or European Union[12].

Scientific, legal and regulatory challenges related to biosimilar manufacturing and development may explain why biosimilar drugs have not lived up to their promise to substantially reduce consumer prices[13,14]. Biologic manufacturing is complex, requiring specialized expertise and a highly controlled environment[15]. Biosimilar manufacturers may lack information about originator biologic manufacturing processes, which are often treated as trade secrets[16]. Many biologics also are protected by multiple patents — time-limited, exclusive rights to use inventions — not only on compositions of matter, but also on manufacturing processes, which biosimilar manufacturers must navigate or challenge[17]. Finally, meeting EMA and FDA approval standards can require 250 or more analytic tests for biosimilars, as compared to about 50 for small-molecule generic drugs[15].

To understand the role that such challenges play in biosimilar manufacturing, we conducted qualitative interviews[18] with national medicines regulators and pharmaceutical manufacturer employees with experience in biologics (Box 1).

Results

In total we conducted 23 interviews with 25 participants (2 interviews were held with each of 2 participants, at their request). Eight participants were EU national medicines regulators and 17 worked for pharmaceutical manufacturers. Of the latter cohort, five worked for manufacturers that marketed only originator biologics, eight for companies that marketed only biosimilars, and four for companies that marketed both originator biologics and biosimilars. Ten pharmaceutical manufacturer participants had expertise in regulatory affairs, four in law, and three in chemistry, manufacturing, and control (CMC) processes (Table 1). The median interview time was just over one hour. Selected perspectives from the interviews, grouped by theme, are shown in Table 2.

Legal barriers: patents and trade secrets. Participants generally perceived trade secrets as a surmountable barrier to biosimilar manufacturing. Participants from biosimilar manufacturers noted that while reverse engineering originator biologics was challenging, the information and expertise necessary to do so were available independent of originator manufacturers. This belief centered on the perception that manufacturing techniques, such as producing the target protein and purifying the product, had become more or less standardized. In addition to using in the development of biosimilars publicly available information from the scientific literature, medicines authority assessment reports, and conference presentations, biosimilar manufacturer participants stated that they benefited from the migration of technical skills when employees switched jobs.

Although disclosure of trade secrets could reveal CMC processes, several regulators and biosimilar manufacturer participants commented that this information was not likely to ease biosimilar development. They stated that such parameters were often exclusively applicable to originator manufacturing facilities because different manufacturers would use different variants of cell lines and nutrients for cell growth to produce the same target protein.

Several participants reported that trade secrets covering the original product helped to spur innovation and increase scientific knowledge. Lacking information on the development of the originator biologic, biosimilar companies are often forced to develop their own processes, resulting in improved understanding of the biologic active substance's characteristics and function. A regulator explained that extensive physicochemical characterization of biosimilars has led to several discoveries of important molecular aspects of active substances, which have resulted in requests to originator companies to change their specifications. For example, another regulator described that for a monoclonal antibody the level of non-fucosylated glycoforms must remain stable because variations can affect the potency of the molecule.

In contrast to trade secrets, participants expressed greater concern over the barriers posed by patents on originator biologics. Originator biologics are protected by more patents than originator small-molecule drugs, including patents that one participant mentioned can block relatively basic

Box 1 | Methodology

Recruitment. Participant eligibility was restricted to current or former US or EU national medicines regulators with experience in biologics and full-time employees of or consultants to pharmaceutical companies with at least one EMA- or FDA-approved originator biologic or biosimilar, who had expertise in CMC processes, law or regulatory affairs. Recruitment was performed via networking and snowballing. No incentives for participation were offered. The Faculty of Health and Medical Sciences at University of Copenhagen approved this study (SUND-2018-09). All participants provided written informed consent.

Interview guide. Interviews were conducted using an interview guide (Supplementary Methods) based on observations from the scientific literature and informal meetings with industry representatives and regulators. Topics entailed establishing biosimilarity and the biosimilar manufacturing process, including the impact of patents, trade secrets and limited disclosure of 'quality-by-design' data. Quality-by-design is a systematic approach to drug development that involves identification of acceptable product variability not affecting product efficacy, safety or quality[30]. For a pharmaceutical manufacturer, this information may be useful for understanding how best to design a product and the robustness of the manufacturing process[31]. Questions were open-ended to allow the participants to shape the direction of the conversation and designed to facilitate approximately one-hour-long interviews.

Interviews. L.C.D. conducted the interviews in person or via telephone[32] between September 2018 and August 2019. Participants did not represent their employer but rather gave their personal views based on their professional experiences. All interviews but one were audio-recorded and transcribed verbatim. Extensive notes were taken during the non-audio-recorded interview. The transcripts and notes were sent to the respective participants for commenting and approval.

Analysis. We performed content analysis on the textual data in the transcripts and notes[33]. Two analysts (L.C.D. and S.K.S.) began coding the data independently by systematically reading the transcripts line by line, considering the meaning of the text, and — if a text segment was considered relevant for the aim — developing and applying a code capturing its underlying theme. L.C.D. and S.K.S. then compared their individual codes and merged these into overarching categories that could capture the meaning of all relevant codes. On this basis they reached a consensus list. L.C.D. used this list to analyze each transcript, sending a subset to A.B.A. for auditing[33]. Thereafter, L.C.D. discussed and interpreted the coding results with A.S. to finalize the analysis.

scientific processes used for multiple purposes. Biosimilar manufacturer participants reported difficulty ascertaining these patents owing to the lack of an efficient search mechanism. Under US law, manufacturers of small-molecule drugs must report select patents to the FDA, which are indexed in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the Orange Book. These patents can be used to identify corresponding European patents. However, originator biologic manufacturers are not required to report similar patents to the FDA. Participants noted that the difficulty in mapping the patent landscape for originator biologics led to considerable uncertainty and risk for biosimilar companies. Finally, the participants mentioned that it was challenging but possible to work around identified patents protecting the originator product.

Regulatory barriers: clarity and uniformity. A key biosimilar development challenge that participants raised was regulatory clarity. Biosimilar manufacturer participants stated that while they knew what biosimilar approval requirements were, they were not always certain how to fulfill them to regulators' satisfaction. Regulators highlighted the merits of such ambiguity, commenting that it helped to avoid reliance on outdated methods and their need for guideline flexibility. To address uncertainty, biosimilar manufacturer participants reported seeking advice from regulators at multiple stages of development. Regulators described biosimilar manufacturers sometimes developing biosimilars in parallel rather than stepwise — for example, conducting biofunctional and clinical investigations before completing physicochemical analyses. Regulators said that manufacturers risk delay and cost overrides if outreach is performed too late in development.

Of special concern was whether clinical trials would be necessary for a particular biosimilar product in development. Two biosimilar manufacturer participants commented that despite demonstrating very close similarity of their biosimilars to reference products, clinical trials were still required to gain approval in the European Union. These experiences fueled the perception that negotiation with the EMA over whether to conduct clinical trials was not possible notwithstanding EMA guidelines permitting trials to be waived.

Biosimilar manufacturer participants also expressed a desire for greater uniformity of requirements between the EMA and the FDA. Although participants perceived many similarities in approaches by the agencies, key differences existed. For example, a regulator specified that the FDA focused on fixed statistics like prespecified acceptable standard deviation between biosimilar and originator products. By contrast, this interviewee explained that the EMA applied statistics on a case-by-case basis. Another biosimilar manufacturer participant echoed this point, noting that companies needed to perform different analyses for each jurisdiction. In general, the manufacturer participants considered the FDA more stringent than the EMA, which a biosimilar manufacturer participant ascribed to the FDA being more cautious toward biosimilars in general.

Discussion

In this study aimed at understanding key scientific, legal and regulatory challenges in biosimilar development and their effect on biosimilar market entry, we found that biosimilar manufacturers and EU national medicines regulators perceived trade secrets as being a surmountable barrier. By contrast, patents protecting originator biologics were considered a greater obstacle given their large number and difficulty in identification. We further observed tension between regulators' need for flexibility in applying guidelines to different cases and manufacturers' preference for certainty concerning biosimilar testing requirements.

Our findings suggest that policies to promote greater disclosure of manufacturing practices may not yield large dividends, even though some scholars — including

Table 1 | Qualitative interview participant affiliations and expertise

Type	Number	Primary expertise		
		Regulatory affairs	CMC	Law
EU national medicines regulators	8	N/A	N/A	N/A
Originator-only manufacturer participants	5	2	2	1
Originator and biosimilar manufacturer participants	4	3	0	1
Biosimilar-only manufacturer participants	8	5	1	2
Total	25	10	3	4

N/A, not applicable.

Table 2 | Selected insights from participants on biosimilar manufacturing challenges

Theme	Quotation
Trade secrets	"I would say trade secrets plays a lower or a low role or are less important because as I said all the details how you develop biologics are public." (biosimilar manufacturer participant)
	"If you look at, for example, developing an antibody, the steps that you do and the processes you do are very, very standardized." (biosimilar manufacturer participant)
	"I don't imagine that having the exact process parameters from the originator would make the day for the biosimilar [developer]." (EU national medicines regulator)
	"You just have to follow all these steps … [however] with the right background knowledge and expertise [in] all these steps you're able to do it" (biosimilar manufacturer participant)
Patent landscape	"We know already a bit [about the] patents that potentially are invoked by the patentee; you can go to the Orange Book … you [can] go back to the international application, and then it falls down to European patents. And then you can proactively identify those European patents. But that is not possible for biosimilars." (biosimilar manufacturer participant)
	"It makes the whole launch of your biosimilar a much riskier business, and one where you never really know whether you'll be safely promoting your product or whether you're exposing yourself to claims … that's a significant business uncertainty." (biosimilar and originator manufacturer participant)
Regulatory clarity and uniformity	"If we write things in the guidelines in too much detail … they cannot develop the field themselves. They get stuck in something that … might be old stuff already." (EU national medicines regulator)
	"You get advice on different moments to make sure that what you're doing is still in line with what they expect. Also I think [it's] sort of strategic to also make sure that the regulators don't change their minds going along the process." (biosimilar manufacturer participant)
	"Of course companies would love that we [in Europe] had, like FDA, an approach saying 'use the statistic called equivalence testing, fulfill it, you must not deviate more than this, then you have a biosimilar'. That would be so much easier for them." (EU national medicines regulator)
	"They [a biosimilar manufacturer] had to address many more items for another [active substance] product. So you can see that [stringency] both on paper, but also in practice, the FDA appears to be a bit more stringent or at least cautious than the EMA." (biosimilar manufacturer participant)

one of the authors — have raised concerns that trade secrets could pose major barriers to biosimilar development and manufacturing[16,19]. The protection offered by trade secrets may also have diminished over time as scientific knowledge has grown and regulators have adopted far-reaching transparency and disclosure policies for clinical-trials data transparency, which have been supported by European court decisions[20,21]. Furthermore, as participants noted, it is uncertain how helpful CMC process disclosure would be, given the different development approaches taken by each manufacturer. However, trade secrets can still pose barriers to manufacturers without established biotechnology experience, as well as for products that are not recombinant proteins.

The main intellectual property concern for biosimilars among the participants was the large numbers of patents — sometimes called thickets — that originator biologic manufacturers obtain relating to their products. Some of these patents can be missed in even a comprehensive search, presenting a major challenge in identifying the processes that must be circumvented to stay clear of litigation. The Biologic Patent Transparency bill — proposed in the US Congress in 2019 — would help address this problem by establishing a mandatory, searchable list for patents protecting biologics, which would be included in the FDA's Purple Book, an analog of the Orange Book[22]. As corresponding European patents could be identified from listed US patents, enactment of the bill would be beneficial for both jurisdictions. In addition to this legislative reform, user-generated solutions for specific technologies, such as the use of patent pools and clearinghouses in synthetic biology and gene editing[23], may prove helpful and warrant further exploration.

Concerning regulatory clarity, the EMA attempted to address existing shortcomings by establishing a pilot project in 2017 that offers biosimilar applicants greater guidance on how to proceed with a viable development plan, including how to design a clinical comparability study to meet regulatory requirements[24]. However, this initiative assumes a stepwise approach to biosimilar development, whereas in practice development is often pursued in parallel. The pilot project also does not resolve the need for companies to seek advice on multiple scientific fronts to keep their biosimilar development aligned with regulatory requirements. A possible solution could be to reduce the financial burden of seeking scientific advice. This would help less experienced biotechnology manufacturers, incentivizing more biosimilar entrants. Another step forward would be for the FDA and EMA to jointly develop biosimilar development guidance. Although both regulators rely on common scientific principles, hold joint meetings and participate in the International Council for Harmonisation[25,26], substantive differences remain, which could be minimized through greater collaboration. Aligning statistical approaches to biosimilar assessment, a goal referenced in both the EMA's Regulatory Science Strategy to 2025 and the FDA Biosimilar Action Plan[27,28], could be one area of focus.

Our study provides insight into key perceptions of biosimilar development and

manufacturing challenges. The diversity of participants, which included regulators and industry participants from manufacturers of originator biologics, biosimilars only, or both originator biologics and biosimilars, was an important strength of the investigation. However, four primary limitations should be noted. First, the extent to which our findings are transferable[29] to other markets, specific sectors and situations, such as vaccine development and manufacturing in health emergencies, or to more complex biologic drugs such as gene therapies, is uncertain. Second, further study in this area should also include the perceptions of US medicines regulators, who were not able to participate in this study. Third, the study did not explore the impact of regulatory exclusivities, which warrants further investigation. Fourth, this study did not focus on the normative question of whether potential barriers posed by trade secrets might be justified from a business perspective.

Conclusions

Primary challenges with biosimilar development and manufacturing include legal and regulatory issues, particularly numerous patents protecting originator biologics and the difficulty in identifying them, leaving biosimilar developers with unnecessary business uncertainties. Policymakers must take measures to resolve this problem to avoid discouraging would-be entrants from developing biosimilars. Regulators should also facilitate more efficient biosimilar developments and develop joint biosimilar guidelines. These measures could create a more vibrant competitive biologics market to provide higher healthcare cost savings, to the benefit of patients.

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Competing interests

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Additional information

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